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Increased risk of *Staphylococcus aureus* bacteremia in hemodialysis – a nationwide study

Hemodialysis vascular access

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Abstract

Introduction *Staphylococcus aureus* bacteremia (SAB) is a high-risk infection and feared complication related to hemodialysis. This study aimed to investigate incidence and risk factors for SAB depending on hemodialysis access type.

Methods The Danish National Registry on Regular Dialysis and Transplantation was used to identify patients from January 1, 1996 to December 31, 2011 with end-stage kidney disease. Information on SAB was obtained from the national SAB Database. Patients were followed until death, the first episode of SAB, or end of study (December 31, 2011). Independent risk factors were assessed by multivariable Poisson regression with time-updated exposure variables.

Findings 9997 patients were included. The initial modality of renal replacement therapy was hemodialysis in 6826 patients and peritoneal dialysis in 2882 patients; 289 patients had pre-emptive kidney transplantation. SAB occurred in 1278 patients (12.8%). The incidence rate of SAB declined after 90 days and leveled off after 270 days in hemodialysis, peritoneal dialysis and kidney transplanted. As compared to peritoneal dialysis, the adjusted rate ratio (RR) for SAB was 7.42 (95% CI 5.63-9.79) in uncuffed central venous catheter (CVC), 5.68 (95% CI 4.39-7.36) in cuffed CVC, 4.43 (95% CI 2.10-9.53) in arteriovenous graft and 3.40 (95% CI 2.79-4.15) in arteriovenous fistula. SAB risk did not differ between uncuffed- and cuffed CVC. The risk of SAB was increased during the first three months of renal replacement therapy especially for CVC (RR 11.37 (95% CI 7.09-18.22)) compared with peritoneal dialysis. Diabetes mellitus (RR 1.35 (95% CI 1.20-1.51)) and male sex (RR 1.15 (95% CI 1.03-1.29)) were also associated with SAB.

Discussion Patients on hemodialysis had a high incidence rate of SAB, particularly those undergoing hemodialysis via CVC. SAB risk was comparable for cuffed- and uncuffed CVC. Diabetes mellitus, male sex, and the first three months in renal replacement therapy in particular CVC were independently associated with SAB.

Keywords

Staphylococcus aureus bacteremia, hemodialysis access type, renal replacement therapy

Background

Staphylococcus aureus bacteremia (SAB) is a serious, common complication of hemodialysis (1-17). Several characteristics contribute to the increased risk of SAB among hemodialysis patients, including the need for repeated invasive procedures, disruption of the skin barrier, and compromised immune system related to uremia (10;18).

Although different forms of hemodialysis intravascular access are known to confer different risks of SAB (15;19), the incidence rate and risk factors for SAB according to the type of hemodialysis vascular access is not well studied.

The aim of this study was 1) to estimate the incidence of SAB according to form of vascular access (uncuffed-, cuffed central venous catheter (CVC), arteriovenous graft and arteriovenous fistula) and 2) to identify risk factors for SAB among hemodialysis dependent patients.

Materials and Methods

Data sources

In Denmark, every resident is provided a permanent identification number at birth or immigration, allowing linkage between nationwide administrative registries at an individual level. In the present study, five of these nationwide registries were assessed. The Danish National Patient Registry was established in 1978 and includes information on diagnoses and procedural codes. Each outpatient appointment and hospital admission is coded at discharge with one primary diagnosis, and if appropriate, one or more secondary diagnoses, all according to the 8th revision of the International Classification of Diseases, and since 1994 the 10th revision (20). The diagnosis codes used to obtain information on comorbidity are considered valid (21). The National Civil Registry contains

information on every death occurring in Denmark. The Danish National Prescription Registry contains information on every dispensed prescription since 1995, including date of purchase, coded according to the Anatomical Therapeutic Classification in Denmark. This registry is considered accurate and valid (22). The Danish National Registry on Regular Dialysis and Transplantation was established in 1990 and holds information on all Danish patients in renal replacement therapy including changes in therapy for end-stage kidney disease and is considered valid (23). The nationwide SAB Database was established in 1956 at Statens Serum Institut. This database registers more than 94% of *staphylococcus aureus* positive blood cultures in Denmark, referred from Departments of Clinical Microbiology all over Denmark (24).

Population

The study population comprised all end-stage kidney disease patients initiating renal replacement therapy in the period from January 1, 1996 to December 31, 2011 assessed via The Danish National Registry on Regular Dialysis and Transplantation. Renal replacement therapy included hemodialysis, peritoneal dialysis, and kidney transplantation (transplantation carried out pre-emptively and after initiation of either hemodialysis or peritoneal dialysis).

End-stage kidney disease patients initiating or changing renal replacement treatment to either peritoneal dialysis or kidney transplantation from hemodialysis were included in the study to allow treatment switch and complete analyses of time spent in hemodialysis during follow-up. Hence, every change in renal replacement therapy modality was identified and entered time-updated, allowing each patient to change renal replacement therapy subgroup (e.g. from hemodialysis to

kidney transplantation, adding risk time to more than one subgroup) during follow-up. For classification of dialysis modality and hemodialysis vascular access type, detailed information including CVC (cuffed and uncuffed), arteriovenous fistula, arteriovenous graft and peritoneal catheter were obtained from The Danish National Patient Registry and combined with primary and changing treatment modalities of hemodialysis, peritoneal dialysis and kidney transplantation from The Danish National Registry on Regular Dialysis. Hemodialysis patients with a failed- or an immature arteriovenous fistula added risk time to a cuffed- or an uncuffed central venous catheter until the arteriovenous fistula was available for hemodialysis. The data were accessed at individual level in collaboration with two independent nephrologists.

Comorbidities

Data on comorbidities were retrieved from The Danish National Patient Registry up to five years before initiation of renal replacement therapy until event, death or study end. The diagnosis of diabetes mellitus was derived from redemption of antidiabetic drugs from The Danish National Prescription Registry.

Outcome

The outcome of interest was the first event of SAB after initiation of renal replacement therapy in the period 1996-2011 and was derived from the nationwide SAB Database. All patients were followed until event, death or study end (December 31, 2011).

Ethics

The present observational registry-based study was approved by the Danish Data Protection Agency (ref. 2007-58-0015 / internal ref. GEH-2014-015 I-suite no. 02733).

Statistical analyses

Continuous data are presented as mean±standard deviation. Differences between categorical variables were analysed with Chi-squared test. Differences between continuous variables were analysed with non-parametric tests. The incidence of SAB was based on the number of events in the study population divided by the time interval spent in each modality of renal replacement therapy. Multivariable Poisson regression was used to determine the association of SAB with each renal replacement therapy modality (hemodialysis, CVC (cuffed and uncuffed), arteriovenous fistula, arteriovenous graft, peritoneal dialysis and kidney transplantation) and to identify independent risk factors for SAB. The model included renal replacement therapy modality time-dependently, allowing each patient to change modality during follow-up (e.g. from hemodialysis to kidney transplantation, adding risk time to more than one subgroup). Sex, age and comorbidities (diabetes mellitus, mitral- and aortic valve disease) were covariates in the models. Comorbidities were entered time-dependently at the time each was noted. Diabetes mellitus was noted at the time glucose-lowering prescription was purchased. The current calendar year was split and entered into the model in bands of five years, and age was included in the model in bands of one year. The model was adjusted for the overall time spent in renal replacement therapy, which was split into time bands of three periods of 90 days, 270 days, and >270 days until event, death or study end. The second period was selected to represent the second quartile distribution of outcome. Poisson trend test was performed to test for significant change in the incidence of SAB across the study period.

Interaction between the modalities of renal replacement therapy and sex, age, calendar year, diabetes mellitus, mitral- and aortic valve disease was tested and found to be non-significant except for the overall time spent in each period of renal replacement therapy. Stratified analysis of overall time spent in each period of renal replacement therapy was performed to assess this interaction. Statistical analyses were performed using SAS version 9.4 (SAS institute, Cary, NC, USA), and $p < 0.05$ was considered significant.

Results

Characteristics of the study population

A total of 9997 patients initiated renal replacement therapy from January 1, 1996 to December 31, 2011. At baseline, 6826 patients initiated renal replacement therapy by hemodialysis, 2882 by peritoneal dialysis, and 289 were pre-emptive kidney transplanted, Table 1 (Supplemental Tables 1 and 2).

Incidence of SAB

A total of 1278 initial episodes of SAB were identified during the study period in the entire cohort of 9997 renal replacement recipients. Hemodialysis accounted for 1119 of the SAB events, peritoneal dialysis for 117 and kidney transplanted for 42. SAB reoccurred twice in 40 patients and three times in four patients. Recurrence of SAB was defined as at least 90 days apart the previous SAB event. The incidence rate of SAB remained constant during the last decade of the study period, Figure 1.

The overall incidence rate of SAB was 19.3/100 person-years in the first 90 days in renal replacement therapy, Figure 2. The incidence rate was significantly higher in hemodialysis (27.4/100 person-years) than in peritoneal dialysis (3.3/100 person-years) and kidney transplant recipients (7.8/100 person-years). The incidence rate was 36.5/100 person-years in the unknown hemodialysis access subset, representing unclassified hemodialysis vascular accesses with unavailable information for further categorization.

The incidence rate of SAB in the first 90 days in hemodialysis patients with uncuffed CVC was 42.6/100 person-years, in cuffed CVC 24/100 person-years, in arteriovenous fistula 23.6/100 person-years and in arteriovenous graft 19.3/100 person-years.

The incidence rate of SAB continued to decrease after 90- and 270 days in every modality of renal replacement therapy.

During the first year in renal replacement therapy, 48.7% of the total number of SAB events occurred in the hemodialysis patients, 4.6% in peritoneal dialysis, and 1.1% in kidney transplanted patients.

At the time of SAB, the hemodialysis vascular access was an arteriovenous fistula in 50.8% of patients, cuffed CVC in 10%, uncuffed CVC in 7.3%, arteriovenous graft in 0.5% and unclassified in 19%.

Factors associated with SAB

Figure 3 shows the results of the adjusted multivariable Poisson regression for the first episode of SAB in the various modalities of renal replacement therapy. The rate ratio (RR) of SAB was 4.10

(95% CI 3.39-4.97) in hemodialysis patients, 0.38 (95% CI 0.27-0.55) in kidney transplanted patients, 4.43 (95% CI 2.10-9.53) in arteriovenous graft, 3.40 (95% CI 2.79-4.15) in arteriovenous fistula, 5.68 (95% CI 4.39-7.36) in cuffed CVC, and 7.42 (95% CI 5.63-9.79) in uncuffed CVC compared with peritoneal dialysis. The risk of SAB did not differ between uncuffed CVC and cuffed CVC (RR 1.29 95% CI 0.99-1.69). In the first three months of renal replacement therapy, the risk of SAB was 5.96 (95% CI 5.25-6.76) and 1.67 (95% CI 1.42-1.96) for 91-270 days compared to >270 days in renal replacement therapy. Diabetes mellitus and male sex were independently associated with SAB with RRs of 1.35 (95% CI 1.20-1.51) and 1.15 (95% CI 1.03-1.29), respectively. The relation between aortic valve disease (RR 1.07 95% CI 0.82-1.38) or mitral valve disease (RR 1.27 95% CI 0.94-1.70) and SAB did not reach statistical significance.

In the first three months in renal replacement therapy, the risk of SAB was 11.37 (95% CI 7.09-18.22) in CVC, 7.22 (95% CI 4.49-11.10) in arteriovenous fistula, and 2.07 (95% CI 0.84-5.08) in kidney transplanted patients compared to peritoneal dialysis, Figure 4.

Ninety-day mortality was 5.6%, whereas the mortality rate in the subsequent period (91-270 days) was 9.2% in the end-stage kidney disease patients.

Discussion

In this nationwide study of end-stage kidney disease patients, the incidence rate of SAB was 4-fold higher in hemodialysis patients regardless of vascular access as compared with peritoneal dialysis. For hemodialysis patients, vascular access type was important. Patients with a CVC had a higher incidence rate of SAB than those with arteriovenous fistula as dialysis access. Of note, risk for SAB

did not differ between uncuffed- and cuffed CVC. In addition, the risk was significantly increased during the first three months of renal replacement therapy compared to >270 days. The first three months in renal replacement therapy constituted a higher risk for SAB in CVC than arteriovenous fistula, with both compared to peritoneal dialysis.

The overall incidence rate of SAB in this end-stage kidney disease study population was considerably higher than in the general Danish population (0.026/100 person-years) (24). This difference might be explained by impaired immune defense related to uremia and repeated access to the vascular system and peritoneum, along with immunosuppressive therapy increasing susceptibility to bacteremia in the end-stage kidney disease population (10;25;26).

In a retrospective case series of 898 patients, Wang et al analysed 366 hemodialysis- and 532 peritoneal dialysis patients with 191 episodes of bacteremia during 2003-2008 at a single hospital (27). Similar to our current data, they found a higher incidence rate of bacteremia in hemodialysis than in peritoneal dialysis. However, patients were censored at switch in treatment modality, at transplantation and at change in dialysis affiliation.

Recently, a Danish study by Nielsen et al reported the overall distribution of SAB incidence rates in end-stage kidney disease patients, with hemodialysis at the high end and kidney transplanted patients at the low end (28). This pattern might be explained by repeated vascular access and the local granulocyte defect at the access site in hemodialysis patients (29), which seems to exceed the risk of bacteremia related to immunosuppressive therapy in kidney transplanted patients. Moreover, Nielsen et al reported a higher overall incidence rate of SAB in patients on peritoneal dialysis than kidney transplant patients. We investigated the SAB incidence rate during three time periods of

renal replacement therapy and found an initial higher SAB rate in kidney transplanted than in peritoneal dialysis patients, which decreased below the rate of peritoneal dialysis after 270 days.

In a recent large retrospective study of US hemodialysis patients, Nguyen et al analysed the incidence rate of overall bacteremia and reported the highest rate in CVCs followed by arteriovenous graft and arteriovenous fistula (30). Arteriovenous graft is applied to a limited extent in Denmark, which leaves the rate inconclusive. However, the CVCs remain the main contributor to high rates of SAB in hemodialysis patients. Taken together, these results emphasize the importance of initiating renal replacement therapy with the establishment of an arteriovenous fistula, reducing the time of CVC access in an effort to decrease SAB events.

Previous studies have addressed the risk of infections in CVC with incongruent results. Two population studies by Stevenson et al (31) and Tokars et al (32) suggested a possible lower risk of infection in cuffed- versus uncuffed CVC. In contrast, Taylor et al (15) found no difference between them. Taylor et al included 527 hemodialysis patients and identified 93 first time bacteremia events from nine hemodialysis units, enrolled from 1998-1999 with a follow-up of 6 months for each patient. Taylor et al censored the patients at switch in treatment modality and at change in dialysis unit. The current results are comparable to the findings of Taylor et al, but our cohort of end-stage kidney disease patients was national, patients were followed up to a maximum of 16 years, were allowed to stay in the study at switch in treatment modality and remained in the study at change in dialysis affiliation.

The mortality rate in hemodialysis patients was remarkably high in the initial period after commencement of hemodialysis. Robinson et al (33) reported mortality rates in patients initiating

hemodialysis of 26.7/100 patient-years in the first 120 days, decreasing to 16.9/100 patient-years and 13.7/100 patient-years at 121-365 days and >365 days, respectively. We found a high mortality in end-stage kidney disease patients after initiation of renal replacement therapy within the first nine months. In a large cohort including 86,886 patients initiating hemodialysis from 11 countries, Jager et al found cardiovascular death as the leading cause of death followed by infections (34). The patients were included from the ERA-EDTA registry during 1994-2007, with a mean follow-up of 1.8 years. We demonstrated a high risk of SAB in CVC and arteriovenous fistula during the initial 90 days of renal replacement therapy, which declined after 90 days and levelled off after 270 days. These results might be explained by the initial high mortality from cardiovascular causes and infections, resulting in a continuous selection for less comorbid patients throughout the initial period of hemodialysis.

Diabetes mellitus and male sex constituted an independent risk factor for SAB in accordance with previous literature (10;35;36).

Strengths and limitations

The study is limited to the observational design. The events in the unknown hemodialysis vascular access subset are most likely a combination of cuffed- and uncuffed CVCs, since arteriovenous graft and arteriovenous fistula require surgical intervention, misclassification is less likely. In addition, the codes denoting the hemodialysis access are not formally validated, thus misclassification concerning the differentiation between cuffed- and uncuffed CVC cannot be excluded even though the procedural codes in the registry were reviewed manually for each individual patient. It should be noted that the cohort of end-stage kidney disease patients is large

and nationwide, including every patient initiating renal replacement therapy in the study period.

Moreover, every change in treatment modality during the study period was tracked at the individual level.

Conclusion

In a nationwide end-stage kidney disease population, the incidence rate of SAB declined after 90 days and leveled off after 270 days in hemodialysis, peritoneal dialysis and kidney transplanted.

The incidence rate of SAB in CVCs was higher than in arteriovenous fistula. SAB risk did not differ between cuffed- and uncuffed CVC. Diabetes mellitus, male sex and the first three months in renal replacement therapy especially in CVC were independent risk factors for SAB. These results emphasize the importance of arteriovenous fistula as the primary vascular access in hemodialysis and strongly suggest limited use of CVCs.

Abbreviations

SAB: Staphylococcus aureus bacteremia, **CVC:** central venous catheter, **RR:** Rate ratio

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Figure Legends

Figure 1. Incidence rate of SAB in renal replacement therapy recipients

Figure 2. The incidence rate of SAB in various renal replacement therapy modalities

*134.6/100 person-years

HD, hemodialysis; PD, peritoneal dialysis; KT, kidney transplantation; T, total; AV-F, arteriovenous fistula; AV-G, arteriovenous graft; C-CVC, cuffed central venous catheter; U-CVC,

uncuffed central venous catheter; Un-HD, unknown hemodialysis; 95% CI, 95% confidence interval

Figure 3. Risk factors for SAB in patients receiving renal replacement therapy

*Model adjusted for sex, age, diabetes mellitus, aortic valve disease, mitral valve disease, calendar time, renal replacement therapy periods (≤ 90 days-, 91-270 days- or >270 days in renal replacement therapy).

†Renal replacement therapy period 1: first 90 days in renal replacement therapy, renal replacement therapy period 2: 91-270 days in renal replacement therapy, renal replacement therapy period 3: >270 days in renal replacement therapy to event, death, or study end.

‡ CVC, central venous catheter, RR, Rate ratio, 95% CI, 95% confidence interval

Figure 4. Risk of SAB in renal replacement therapy according to time in renal replacement therapy

*Model adjusted for sex, age, diabetes mellitus, aortic valve disease, mitral valve disease, and calendar time

95% CI, 95% confidence interval